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Via e-mail, fax, and first class mail

Dr. Barbara Shane
Executive Secretary
NTP Board of Scientific Counselors
NTP Liaison and Scientific Review Office
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Dear Dr. Shane:

We are hereby submitting, for consideration at the Board's meeting on August 18, 2005, pursuant to 70 FR 38145 (July 1, 2005), comments on the implications of the OMB information quality peer review guidance for the NTP Report on Carcinogens program.

Basic attributes of peer review under the OMB guidance

The basic attributes of peer review of agency scientific assessments under the OMB guidance, with the degree of emphasis on the attributes depending on the importance of the assessment, are the following:

independence of reviewers
expertise of reviewers
transparency
public participation

OMB "prompt letter" on improving peer review of RoC assessments

One month before OMB issued its final guidance, the Administrator of OMB's Office of Information and Regulatory Affairs sent an OMB "prompt letter" to the NIH Director to make

several suggestions for improving the transparency of peer reviews specifically for the Report on Carcinogens ("RoCs").[1] The letter indicated that those "prompt" comments were being given to NIH in view of the degree of controversy being generated by the RoCs as evidenced by the unusual number of information correction requests (six) for the RoCs which had already been filed pursuant to the HHS information quality guidelines of September 2002.

OMB recommended that for all RoC reviews the following steps be added to the review procedures:

(1) a document containing agency responses to public comments on the nomination that would be made available to the public and to peer reviewers prior to their review

(2) updates to the Background Document to incorporate technical comments from peer reviewers and agency responses to the peer review comments

(3) external peer review of listing profiles (the actual text accompanying the RoC listing, as opposed to the Background Document) before a new RoC is sent to the Director and Secretary for approval.

The importance of determining whether an RoC assessment is "influential" or "highly influential", or neither, under the OMB guidance

A major threshold issue for application of the OMB peer review guidelines to the RoCs is whether the assessment should be considered to be a an "influential scientific assessment"("ISA") or a "highly influential scientific assessment" ("HISA"), or neither. The procedural RoC issues raised by the new guidelines differ significantly depending on which category an assessment is assigned to, as explained below.[2]

ISA definition: The agency can reasonably determine that the assessment will have, or does have, a "clear and substantial impact on important public policies or private sector decisions".

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[1] The OMB prompt letter can be accessed at http://www.whitehouse.gov/omb/inforeg/prompt/nih_ntp111604.pdf. As explained on the OMB website, "[t]he purpose of the prompt letter is to suggest an issue that OMB believes is worthy of agency priority. Rather than being sent in response to the agency's submission of a draft rule for OIRA review, a "prompt" letter is sent on OMB's initiative and contains a suggestion for how the agency could improve its regulations." http://www.whitehouse.gov/omb/inforeg/prompt_letter.html. A copy of the OMB prompt letter is attached to the mailed version of these comments.

[2] Proposed categorization of an upcoming assessment will be announced every six months by an agency under the "planning" requirements of the guidelines.

HISA definition: The assessment could have a potential impact of more than $500 million in any year, or is "novel, controversial, precedent-setting or has significant interagency interest".

It seems obvious that many of the RoC assessments will meet the ISA definition; but, at least at first glance, the HISA definition appears very restrictive because of the $500 million figure. However, the HISA definition should be interpreted as far less restrictive than it might appear on the basis of the $500 million figure. As OMB/OIRA Administrator Graham explained at the American Bar Association conference to discuss the new peer review guidelines that was held on February 23, 2005, the narrative portion of the definition is intended to be more important than the $500 million. Since this is the case, there are likely to be a significant number of RoC assessments which should be categorized as HISA.

The potential disparities between RoC assessments as ISA, HISA, or neither, are a consequence of both the nature of the RoC listings and the inherent problems in estimating economic impacts, both direct and indirect. RoC listings encompass substances with very limited application, such as speciality pharmaceuticals and pesticides which are no longer registered or have very limited uses, to substances which result in wide population exposures and affect numerous entities, industry sectors or components, and companies. Some recent examples of the latter would include naphthalene, asphalt fumes, talc, and atrazine

The nature of the RoC listings is that they do not have direct regulatory impacts, but nevertheless trigger, or are likely to trigger, numerous regulations at the federal, state, and local (and perhaps even international) levels and influence significantly consumer perceptions and choices. The recent U.S. Circuit Court decision in *Tozzi v. HHS* emphasized the indirect impacts of the RoC listings. The court described the RoC listings as "highly influential" and explained that "[w]hen a government attaches an inherently pejorative and damaging term such as 'carcinogen' to a product, the probability of economic harm increases exponentially." 271 F.3d 301, 309 (D.C. Cir. 2001). The court found the RoC listings to be judicially reviewable because they triggered, or were likely to trigger, federal, state, and local regulatory restrictions. Listing of a substance as a carcinogen also can also lead to onerous litigation, with the result that a substance is likely to completely disappear from the marketplace. Such impacts are impossible to estimate in monetary terms, even though their impacts may be very large.

A good number of the RoC listings, in addition to having economic and societal impacts that are difficult to estimate in monetary terms, should be considered as meeting the narrative portion of the HISA definition -- "novel, controversial, precedent-setting" or of "significant interagency interest". Such potential listings should be of interest to the Board, since the proposed listings might meet the narrative portion of the HISA definition not because the listing itself is likely to have substantial economic or societal impacts, but because it raises scientific issues which are "novel, controversial, precedent-setting" or of "significant inter-agency interest". Past examples would include saccharin and TCDD.

Compliance issues raised by the current RoC review process

The current RoC review process – with its multiple levels of review by different groups under different conditions -- does not fit neatly into the usual peer review paradigm and presents a challenge concerning which the agency could certainly benefit from the advice of the Board.

Assessments determined to be "influential" ("ISA"s)

1. The guidance requires that reviewers shall not have participated in the development of the work product to be reviewed. In the past, members of RG1 and RG2 have apparently been identified in the RoCs as having participated in the development of the Draft Background Document. (See, *e.g.*, Appendix D of the 11th RoC.) It also appears that at times agency personnel listed as "alternates" for the principal NTP Executive Committee members have participated in both RG2 and Executive Committee meetings, or have been involved with the development of the work product and participated in Executive Committee meetings. According to explanations previously provided by NTP, even when an alternate does not attend the Executive Committee meeting, that person is likely to have been involved in briefing the principal members, and the principal member will largely rely on the alternate's views (or perhaps even the views of other staff who were involved in previous review meetings or preparation of the assessment).

2. The guidance requires that peer reviewers prepare a report describing their review and their findings and conclusions. RG1 and RG2 currently prepare very abbreviated reports which are appended to the draft Background Document, and such reviews often do not address key issues raised in public comments which were likely to have been, or should have been, considered. The RoC Subcommittee of the Board does not prepare a report. While a transcript of the RoC Subcommittee discussion is made available to the public, and some members provide very brief explanations of their votes when polled at the end of the meeting, it is difficult to consider the transcript to be a "report" which summarizes the determinative views of the subcommittee as a whole on the key issues. The NTP Executive Committee does not prepare a report. There have been various descriptions of NTP Executive Committee meetings. Apparently the meetings are relatively brief, with sometimes 7 or 8 assessments considered within several hours; and it has been explained that the committee members undergo substantial briefing and preparation before attending the meeting. On the other hand, it has been stated that the role of the Executive Committee is limited to consideration of any policy issues raised by the reviews rather than a review of the scientific issues.

3. The guidance requires that reviewers be selected on the basis of expertise. In the past, it appears to have been ordinarily the case that reviewers were selected based on agency affiliation and position rather than special expertise essential to the particular exposure under consideration. On the other hand, there appears to have been increased use of substance-specific expert consultants to assist review committees and aid in the preparation of the assessment, but they apparently do not vote (See Appendix D to the 11th RoC.)

Assessments determined to be "highly influential"

1. The guidance requires that reviewers not be employed by the "sponsoring agency", with narrow exceptions. In the case of the RoCs, the "sponsoring agency" is actually the several agencies within HHS comprising the NTP – NIEHS/NIH, NIOSH/CDC, and NCTR/FDA. It is difficult to view the "sponsoring agency" as limited to NIEHS, even though the initial nomination might indicate it was proposed by NIEHS, since the nominations are approved by an official who is both the Director of NIEHS and Director of NTP, and the RoC program is identified by HHS as an NTP program. At present, three of the four RoC review groups – RG1, RG2, and the NTP Executive Committee, contain employees of NIEHS or NTP. Although the NTP Executive Committee includes federal employee from several agencies outside the NTP, they nevertheless effectively act as employees of NTP when they meet as members of the NTP Executive Committee.

2. The guidance requires that the agency consider soliciting nominations for reviewers from the public, including scientific and professional societies. At present, it does not do this.

3. The guidance requires that the agency prepare a detailed response to the peer review report which contains certain elements outlined in the OMB guidance. At present, NTP does not prepare such a written response, nor do all the peer review groups prepare a report to which the agency could respond. As noted previously, RG1 and RG2 currently prepare very brief and conclusory reports which are appended to the draft Background Documents, and neither the RoC Subcommittee nor the NTP Executive Committee prepare a report (although the a transcript of the RoC Subcommittee public meeting is made available, and some members provide brief explanations following the voting).

4. Reviewers are to be selected based on expertise, and agencies are to avoid repeated use of the same reviewers for multiple assessments, if possible. While the agency appears to be increasingly making use of substance-specific expert consultants, the consultants are not voting members of the committees.

Recommendations

BOSC role

1. The Board should review and comment on any agency plans for revising its RoC peer review process.

2. The Board should review new RoC nominations in order to advise the agency on whether they raise scientific issues which are novel, controversial, precedent-setting or of interagency interest for purposes of making a determination of whether an assessment should be considered HISA.

3. The Board (or its RoC Subcommittee) should review RoC listing profiles before they are submitted to the Director and Secretary.

4. The Board should review new nominations in order to advise the agency on whether a particular review should involve special expertise, and if so what kind, and also consider recommending specific experts and/or recommend that the agency solicit nominations for those areas of expertise from the public, including particular scientific or professional societies. This can be accomplished by having the Board review the agency peer review plans required every six months for this purpose before they are published.

Reviewer roles

1. RoC review committee membership must be revised to ensure that, in the case of ISAs, a reviewer was not involved in the preparation of the draft Background Document, and in the case of HISAs, is not employed by one of the NTP agencies. (RG1 might be eliminated completely as a review committee, so that NIEHS members can participate in preparation of the draft Background Document.) There should not be any overlap between the membership of the review committees.

2. Review committees should prepare and disseminate more detailed reports of their reviews.

Agency roles

1. The agency should solicit advice/nominations for reviewers when specific expertise is required, from both the Board and the public, including scientific or professional societies.

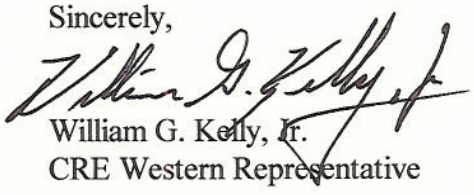
2. The agency should always prepare a response to public comments and peer review comments, and disseminate both, before passing on the assessment to a different review committee or preparing a final recommendation on listing.

3. At each stage of review, and before a final listing determination, the agency should advise the public and reviewers of any changes to the Background Document it is adopting.

4. The agency should submit listing profiles to the Board (or its RoC Subcommittee) for review before submission to the Director and Secretary.

Thank you for your consideration of these comments and recommendations.

Sincerely,



William G. Kelly, Jr.
CRE Western Representative

Attachment (OIRA letter of Nov. 16, 2004 to Director of NIH)

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
WASHINGTON, D.C. 20503

ADMINISTRATOR
OFFICE OF
INFORMATION AND
REGULATORY AFFAIRS

November 16, 2004

Dr. Elias A. Zerhouni
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Dear Dr. Zerhouni:

I greatly appreciated your recent visit with us to talk about the proposed NIH Public Access Policy. We strongly support your commitment to increase both the transparency of and access to NIH funded research.

With regard to transparency I would like to bring to your attention some concerns I have regarding the National Toxicology Program (NTP) that is administratively located at NIEHS/NIH.

Under the Information Quality Act, the National Toxicology Program (NTP) has already received six distinct information quality correction requests related to either the NTP Report on Carcinogens or to the NTP review process for individual substances. These correction requests have brought to my attention concerns about how NTP handles comments from the public and scientific advisors. While NTP already has a rigorous process of scientific deliberation, I would like to make three suggestions that, based on experience at other Federal agencies, are likely to further instill public confidence in the NTP process and the Report on Carcinogens.

First, when NTP receives comments from the public on substances being reviewed for listing or delisting in the Report on Carcinogens, NTP should prepare a response-to-comments document and make this document available to the public in a timely manner. The Report on Carcinogens already acknowledges that "opportunities for public comment and participation are an integral part of the review process." To fully realize the value of the comment process, NTP should prepare and disseminate a response-to-comments document before completion of a substance's review. This document would improve the transparency of the process and assure the public that their perspectives have not only been sought but also considered. Moreover, the discipline of preparing this document will ensure that the scientists responsible for the Report on Carcinogens have systematically considered and addressed all the significant scientific comments that NTP has received. It would also be desirable for this document to be made available before an NTP review committee evaluates a particular substance. With this structure, the members of these important committees will also have the benefit of both the insights of the public and the NTP's responses to these comments.

Second, when the NTP review committees (e.g., RG1, RG2 and Board of Scientific Counselors) provide technical comments to NTP staff aimed at improving an NTP background document, the NTP staff should prepare an updated version of the background document -- including responses to comments from these science advisors -- before final decisions on particular substances are made. Making these updated documents publicly available would reassure everyone that listing decisions are based on a supporting document that has addressed concerns raised by both the NTP's science advisors and the public.

Finally, I suggest that the substance profiles, which appear in the biennial Report on Carcinogens, be reviewed by external reviewers, perhaps the Board of Scientific Counselors, before being finalized. This layer of review would ensure that the writers of the profiles have incorporated the concerns and issues brought forth by the multiple review groups and have correctly captured and appropriately framed the information that needs to be in the final document of record.

I make these suggestions now because we are aware that NTP is already in the process of evaluating and modernizing the process used to prepare the Report on Carcinogens. Although implementing our three suggestions will require some additional staff work in the near term, we believe there may be resource savings in the long run. In any event, we believe the benefits in public transparency and agency accountability justify the additional staff effort.

I encourage you to consider these suggestions during your ongoing deliberations. My staff is eager to work with you on these suggestions.

Sincerely,

John D. Graham, Ph.D.
Administrator